Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Clinical features and outcomes of neonatal COVID-19: A systematic review

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We read with interest the recent article by Badal et al. highlighting clinical characteristics of 1810 paediatric COVID-19 cases. While we agree that children have a better prognosis [1], the neonatal population, as opposed to older children, is susceptible to vertical transmission of SARS-CoV-2 [2], which includes in-utero, intrapartum and early postnatal infection [3].

We aimed to determine the clinical manifestations of neonatal COVID-19 and outcomes based on severity groups. We conducted a systematic review (CRD42020183500) and searched Embase, PubMed, and China Knowledge Resource Integrated (CNKI) from 01 December 2019 to 01 August 2020, using the terms "infant", "newborn", "SARS-CoV-2″, "COVID-19″ and variants (Supplemental Material 1). Additional studies were identified from references of included studies and the John Hopkins Centre for Humanitarian Health database. Studies reporting neonates (≤ 28 days old) who tested positive for SARS-CoV-2 by reverse transcriptase PCR (RT-PCR) were included. Descriptive statistics were used to compare mild-moderately ill neonates (non-severe group) with severe-critically ill neonates (severe group). Grouping was based on World Health Organization's definition [4].

We reviewed 199 full-text articles; 67 studies fulfilled the inclusion criteria (Fig. 1). Quality assessment scores were moderate for the 52 case series (mean = 3.06) and 15 cohort studies (mean = 5) included (Supplemental Material 2). Of 99 neonates diagnosed with COVID-19 infection, 27 (27.3 %) were asymptomatic. Amongst symptomatic neonates, respiratory symptoms were common — dyspnoea (36.1 %), nasal symptoms (19.4 %), cough (18.1 %); 55.6 % had fever. Thirty neonates (30.3 %) had severe-critical illness. Compared to the non-severe group, more neonates in the severe group were symptomatic (100 % vs 60.9 %, $p < 0.001$), admitted to the intensive care unit (91.7 % vs 41.7 %, $p < 0.001$), had dyspnoea (66.7 % vs 14.3 %, $p < 0.001$) and abnormal chest radiographic findings (84.6 % vs 61.5 %, $p = 0.038$). Mild-moderately ill neonates had increased incidence of fever (69.0 % vs 36.7 %, $p = 0.006$) and gastrointestinal symptoms (26.2 % vs 3.33 %, $p = 0.01$). Laboratory findings were similar between these two groups (Table 1).

Similar to older children, neonates with dyspnoea were more likely to develop severe illness [5]. However, diagnosis of severe illness may be confounded by co-existing respiratory diseases present in many neonates with critical COVID-19. Contrary to adults [6], presence of fever did not predict for more severe disease in neonates.

The angiotensin-converting enzyme 2, a major virus receptor, is expressed in the gastrointestinal tract. Thus, in children, gastrointestinal symptoms were correlated with critical illness [7]. However, in our review, gastrointestinal symptoms were associated with milder illness. Amongst 11 mild-moderately ill neonates displaying gastrointestinal symptoms, 10 did not have dyspnoea. We postulate that the presence of gastrointestinal symptoms alone predicts a better prognosis, while gastrointestinal symptoms with dyspnoea predicts a worse outcome, as in adults [8].

Prognosis of COVID-19 neonates were favourable, with no serious complications or mortalities reported. However, included studies were of moderate quality, with incomplete reporting of clinical and investigation results. Additionally, asymptomatic or mildly ill neonates could have been underdiagnosed and hence unaccounted for. As the pandemic evolves, prospective [9] and more systematic reporting of cases will improve our understanding of neonatal COVID-19 and verify utility of symptoms and laboratory tests in predicting disease severity.

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Author contributions

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Abbreviations: CNKI, China knowledge resource integrated; RT-PCR, reverse transcriptase PCR.

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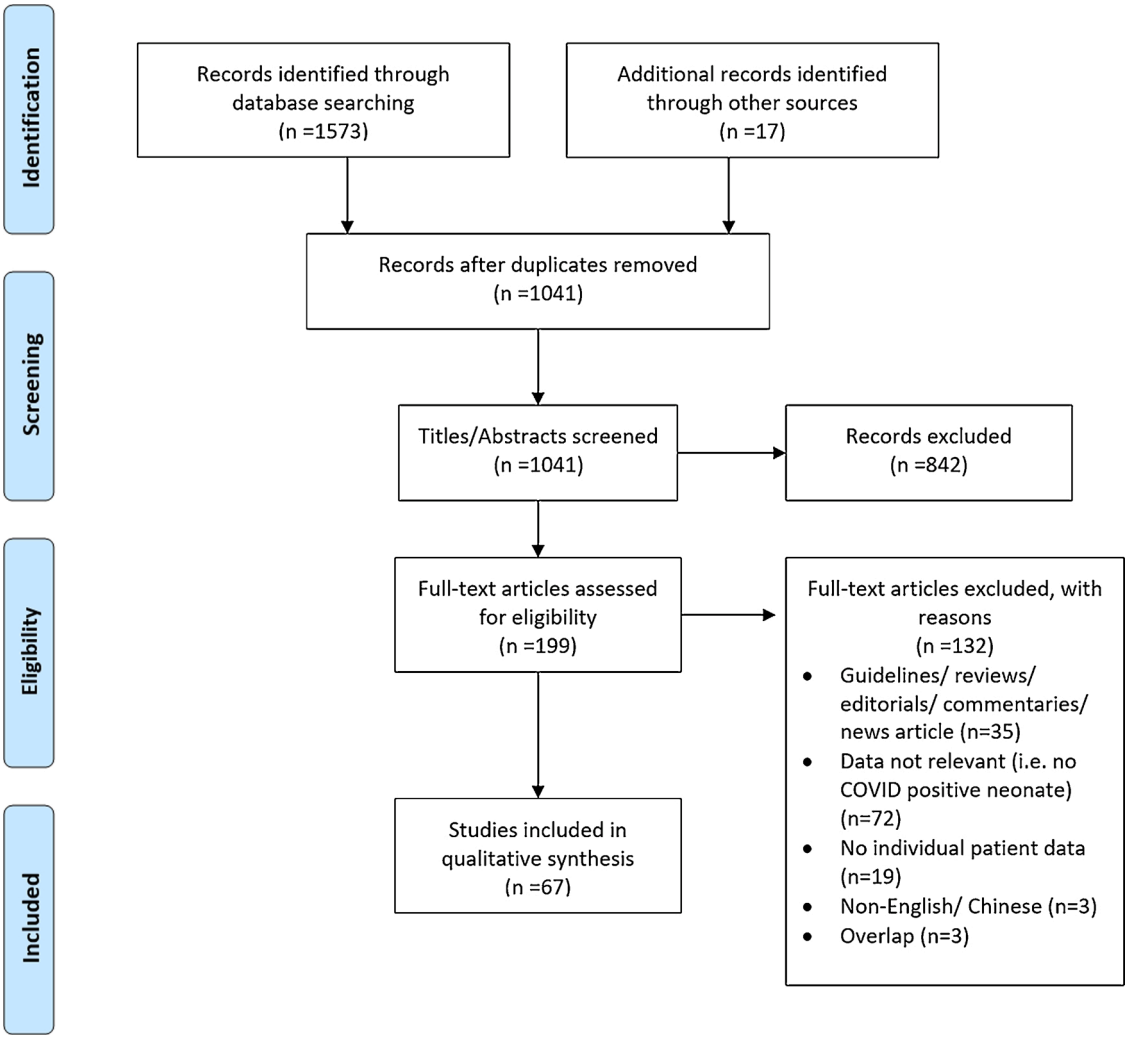

Fig. 1. PRISMA Flow Chart.

Table 1
Neonates with COVID-19 diagnosed by positive RT-PCR test.

	Mild/moderate condition Non-severe group (n = 69)		Severe/critical condition Severe group (n = 30)		p value
	N	%	N	%	
Gestational age at birth, weeks					
≥ 37	33/40	82.5	15/24	62.5	0.128
32 to < 37	4/40	10.0	8/24	33.3	
28 to < 32	2/40	5.0	1/24	4.2	
<28	1/40	2.5	0/24	0.0	
Age at diagnosis, days (median, IQR)	7 (2–17.5)		6 (2–13.75)		0.692
Birth weight, g (median, IQR)	3120 (2743–3470)		2930 (2520–3370)		0.408
Gender					
Male	27/41	65.9	17/27	63.0	0.807
Female	14/41	34.1	10/27	37.0	
Symptomatic	42/69	60.9	30/30	100.0	<0.001*
Symptoms in symptomatic neonates					
Fever	29/42	69.0	11/30	36.7	0.006*
Dyspnoea (apnoea, tachypnoea, hypoxia, cyanosis, chest retractions, increased work of breathing, desaturation)	6/42	14.3	20/30	66.7	<0.001*
Cough	9/42	21.4	4/30	13.3	0.379
Nasal symptoms (congestion, stuffiness, discharge, sneezing)	10/42	23.8	4/30	13.3	0.268
Gastrointestinal symptoms (diarrhoea, vomiting)	11/42	26.2	1/30	3.33	0.01*
Feeding problems	11/42	26.2	12/30	40.0	0.215
Laboratory and radiological findings					
Leukopenia (<5.0 × 10^9/L)	3/23	13.0	4/19	21.1	0.488
Leukocytosis (>19.0 × 10^9/L)	1/21	4.76	1/16	6.25	0.843
Lymphopenia (<3.0 × 10^9/L)	11/24	45.8	7/17	41.2	0.767
Thrombocytopenia (<200 × 10^9/L)	1/15	6.67	2/14	14.3	0.501
Elevated C-reactive protein (>10 mg/L)	2/19	10.5	3/19	15.8	0.631
Elevated procalcitonin (>0.5ug/L)	1/13	7.69	2/8	25.0	0.271
Elevated D-dimer (>0.5ug/mL)	1/1	100.0	4/4	100.0	NA
Elevated serum lactate dehydrogenase (>860 u/L)	0/4	0.0	2/3	66.7	0.143**
Chest X-Ray or Computed Tomography or Lung Ultrasound					
Normal findings	10/26	38.5	4/26	15.4	
Suggestive of pneumonia	16/26	61.5	18/26	69.2	0.038*
Other findings, not of pneumonia	0/26	0.0	4/26	15.4	
Clinical outcomes					
Intensive care unit (ICU) admission	15/36	41.7	22/24	91.7	<0.001*
Duration of hospital stay (median, IQR)	7.5 (2–16)		8 (4.5–18)		0.143
Survival	60/60	100.0	28/28	100.0	NA

* Significant at $p<0.05$, Chi-square test.
** Fisher's Exact test.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2021.104819.

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